Remarks

This Response is provided in response to an Office Actions mailed September 30, 2003 and January 8, 2004.

Claims have been renumbered by the Examiner, and amendments to claims 21 and 23 are made to correct dependency upon the renumbered claims. Claims 1-12 and 20-28 are currently pending in this application. Status identifiers for Claims 20-28 have been reviewed, and if necessary, amended to comply with Office procedures. Claims 10-12 and 20-28 stand rejected under 35 U.S.C. §112, first paragraph and Claims1, 2, 4-6, 8, 11 and 12 stand rejected under 35 U.S.C. § 102(b). This Response is filed to provide a complete reply to all current rejections.

I Claim Rejections

Claims 1-12 and 20 - 28 stand rejected under 35 U.S.C. §112, first paragraph as not being enabled. The Examiner's rejection is based on the assertion that the animal system used by the Applicants is not a recognized model.

Applicants respectfully submit that the phenomena of intrauterine undernutrition and sequelae in adults are common to numerous mammals, including rats and humans. The specification at page 1 describes prior studies of Barker et al, who found that there are "well recognized long term sequelae of persistent growth failure, disordered fetal growth is associated with a higher incidence of hypertension, cardiovascular, cerebrovascular and metabolic disorders in adulthood." Specification, page 1, lines 18-21. Moreover, the phenomenon was described in rats by Woodall et al., Chronic Maternal Undernutrition in the Rat Leads to Delayed postnatal Growth and Elevated Blood Pressure in Offspring. *Pediatr. Res.* 40:438-443 (1996) cited in specification at page 1, lines 23- 25.

Additionally, effects of growth hormone on cardiovascular dysfunction were described in rats in PCT/SE97/01957.

Furthermore, the Barker reference (Hormone Res 42:223-230 (1994) cited in previous Office Action as "Baker", states:

> Third, animal experiments show that changes in nutrition in early life can permanently change the growth and form of the body and a whole range of its structures and functions. Page 223, column 1 to top of column 2.

Additionally Barker cites to several references that reported studies of non-human animal systems, including rats. The references include (numbered according to Barker) (4) Winick et al., Cellular response in rats during malnutrition at various ages. *J. Nutr.* 89:300-306 (1966), (32) Langley et al., Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. *Clin. Sci.* 86: 217-222 (1994), (45) McCrabb et al. Maternal undernutrition during mid-pregnancy in sheep: Placental size and its relationship to calcium transfer during late pregnancy. *Br. J. Nutr.* 65: 157-168 (1991) and (46) McCrabb et al. Maternal undernutrition during mid-pregnancy in sheep: variable effects on placental growth. *J. Agric. Sci.* 118:127-132 (1992).

Applicants especially note the Langley et al article, which describes the same phenomenon in rats as do the Applicants, namely that fetal undernutrition leads to increased systolic blood pressure. Applicants also submit that the Examiner's reliance on the specific conditions of the Applicants' studies (e.g., maternal undernutrition 30% of *ad libitum*, after weaning, pups fed 70% of normal *ad libitum*, day 90, systolic blood pressure was taken, and thereafter, growth hormone was administered), rather than indicating lack of enablement, actually provides substantial enablement by disclosing the exact protocols followed, thereby permitting workers of skill to duplicate the conditions of the studies. The fact that no prior art reference teaches this level of detail in exactly the same way cannot result in the limitation of the "model" to those exact conditions. As stated above, the adult sequelae of intrauterine undernutrition are common among mammals, and are widespread, and not limited to a particular protocol of study.

Therefore, Applicants respectfully submit that rats, including Wistar rats used in the instant studies, are an art-recognized system for studying effects of intrauterine undernutrition and effects of growth hormone on systolic blood pressure.

Regarding the Examiner's comment on page 4 relating to diagnosis of intrauterine under-nutrition, Applicants respectfully submit that the it is well known in the diagnostic arts to take a patient's history, and to use that history in making diagnoses. Intrauterine undernutrition can be diagnosed by finding one or more factors including: (1) maternal factors: maternal malnutrition, placental dysfunction, maternal alcohol abuse, smoking, drug abuse, anaemia, chronic hypertension, pregnancy-induced hypertension, diabetes mellitus, pre-pregnancy weight of less than 50 kg, cyanotic heart disease, connective tissue disease and the like; (2) fetal ischemic or hypoxic episodes, presence of fetal infections, uteroplacental risk factors, and the like, (3) genetic disorders, including dwarf syndromes, chromosomal abnormalities (e.g., trisomies 13, 18 and 21), congenital anomalies (e.g., gastroschisis), mullerian anomalies (e.g, septate uterus), placental insufficiency and the like; and (4) the patient's birth weight below about the 10th percentile for gestational age or a birth weight 2 standard deviations below the mean for gestational age would indicate intrauterine malnutrition; . In particular, a significant finding in patients subjected to intrauterine undernutrition is the finding of low birth weight based on gestational age.

Regarding the diagnosis of "growth retardation", or an "adverse post-natal environment," Applicants respectfully submit that practitioners of skill in the art of diagnosis can use body mass index (BMI). A BMI that is abnormally low or abnormally high, according to industry standards, would be indicative of "growth retardation" or "adverse post-natal environment." Thus, Applicants submit that the diagnosis of growth retardation is well known in the art.

Regarding the Examiner's comment on page 6, relating to dosing, Applicants respectfully submit that finding an effective dose of growth hormone is well within the practitioner's arts. Applicants submit that a medical practitioner would first identify a very low dose based on animal studies, such as those disclosed in the instant application. If administration of that dose did not have the desired therapeutic effect, a practitioner could increase the dose two-fold progressively, until a desired dose that achieved the desired therapeutic effect was observed. Thus, Applicants submit that exact dosing regimens or dose levels are needed to enable this application.

In particular, Applicants submit that Wistar rats have been used previously to study hypertension. As noted above, the phenomena associated with intrauterine undernutrition occur in many different species of mammals, including humans, sheep and rats. Thus, no undue experimentation would be necessary to translate the disclosures and teachings of the instant specification and the figures to therapeutic uses in mammals, including humans.

Thus, from the foregoing, Applicants respectfully submit that the claims are fully enabled to persons of skill in the art without undue experimentation and with a reasonable likelihood of success.

II. Rejections Under 35 U.S.C. § 102

Claims 1, 2, 4-6, 8, 11 and 12 stand rejected under 35 U.S.C. § 102(b) as anticipated by Johannsson et al., J. Clin. Endocrinology and Metabolism (1997) or PCT/SE97/00601 (1997) ("Johannsson").

Applicants note that Johannsson discloses the use of growth hormone (GH) to alter diastolic blood pressure in obese men, but does not demonstrate any effect on systolic blood pressure.

Applicants also note that the blood pressure of the obese men in Johannsson was not elevated, and thus the patients were not hypertensive. Next, Applicants note that diastolic and systolic blood pressure do not necessarily track each other, in that vasodilation typically can reduce diastolic blood pressure, but that an increased stroke volume or increased cardiac contractility can increase systolic blood pressure. For example, Applicants submit that it is commonly known that epinephrine is a drug commonly used to treat patients with shock, that is, with reduced blood pressure. Applicants submit that it is well known that at certain doses, epinephrine causes both increased stroke volume, increased systolic blood pressure, yet at the same dose can be a vasodilator. Furthermore, Johannsson provides no direct association between changes in diastolic blood pressure and systolic blood pressure, in that in the obese subjects studied, although diastolic blood pressure was reduced by therapy, there was no change in systolic blood pressure.

Further, Applicants submit that it is now known in the art that systolic blood pressure is of greater clinical significance than is diastolic pressure. Izzo et al. (Hypertension 35:1021-1024 (2000) (copy included herewith as Appendix 1), has indicated that systolic blood pressure is the most important factor in diagnosis of clinically relevant hypertension in older patients. Page 1022, right column second and third full paragraphs. According to Figure 1 on page 1022, left column, diastolic blood pressure increases with age until the age of about 55 or 60, and thereafter decreases. The age-related decrease in diastolic blood pressure, according to Izzo, correlates inversely with cardiovascular risk. "Risk stratification for major complications of hypertension (stroke, myocardiual infarction, heart failure, and kidney failure) is actually confounded by the use of diastolic BP; in older people with systolic hypertension, diastolic BP is inversely related to cardiovascular risk." Page 1021, left column second full paragraph. In contrast, systolic blood pressure increases with age until about age 80 years. Thus, lowering systolic blood pressure is associated with better clinical outcomes in cardiovascular disease, whereas lowering diastolic blood pressure may actually be associated with poorer outcomes. "For example, systolic hypertension is the most prevalent risk factor in heart failure, and clinical trials have demonstrated unequivocally that control of systolic hypertension prevents the development of heart failure." Page 1021, right column second full paragraph.

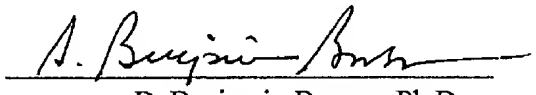
Thus, not only does Johannsson provide no disclosure of any effect on systolic blood pressure, and thereby cannot anticipate Applicants' claims, Applicants submit that Johannsson actually teaches away from Applicants' disclosure of decreasing systolic blood pressure, because decreasing diastolic blood pressure may lead to worse clinical outcomes, and thus cannot form the basis of a rejection on the grounds of obviousness under 35 U.S.C. §103.

Finally, Applicants submit that in view of the above comments, that intrauterine undernutrition is an important aspect to the diagnosis and therapeutically effective treatment of systolic hypertension, and that thus, the preamble to claim 1 "breathes life and meaning into the claim" and has patentable weight.

Based on the arguments presented herein, Applicants respectfully request the Examiner to reconsider the rejections and find the claims allowable. If the Examiner believes that a discussion with the undersigned Attorney would be helpful in addressing these issues, the undersigned invites the Examiner to call at the telephone number below.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 06-1325 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: May 11, 2004 By: 

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